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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,168	09/24/2003	Krista Evans	0942.402003	5379

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,168	EVANS, KRISTA	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 24 September 2003 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7/9/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of application 09/472,065 now US Patent 6,638,732.

Claim 1 is pending.

Drawings

The drawings filed September 24, 2003 are objected to because the y are numbered starting from Figure 5, etc. while said drawings should be designated Figure 1 – Figure 8. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following. Figures 1-4 are described on page 15 in the "Brief Description of the Figures" while there are no such figures in the application.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a genus of DNA molecules encoding a mutant Green Fluorescent Protein (GFP) from any source. Said genus comprises a subgenus of DNA molecules encoding a mutant GFP from *Aequorea victoria.* The amino acid sequence of the wild type GFP from *A. victoria* is 238 amino acids long. An amino acid sequence of a mutant GFP comprises a substitution at positions 64 and 65. Thus, an undefined number of additional substitutions is allowed. Therefore, such DNAs encode a genus of mutant GFPs with different fluorescent properties and having different structures. The specification does not contain any disclosure of the properties of all DNA sequences

that encode mutant GFPs modified at positions 64 and 65. Thus, the genus of DNAs that comprise these above DNA molecules is a large variable genus comprising DNAs encoding many different fluorescent proteins. Therefore, many functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only two species of the claimed genus of DNAs encoding mutant GFPs, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus (DNAs encoding SEQ ID NOs: 5 and 6, A1 and A4 GFP mutants, respectively). One skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNAs encoding GFP mutants that differ from the wild type *A. victoria* GFP by mutations at positions 64 and 65, including SEQ ID NOs: 5 and 6, does not reasonably provide enablement for DNAs encoding GFP mutants having an undefined homology to SEQ ID NOs: 4, 5 or 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Despite knowledge in the art to produce mutations in proteins, the specification fails to provide guidance as to where, and what type of (i.e., what amino acid to substitute into the known sequence), changes in amino acid residues will result in the increased ability to fluoresce under white light. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Mutations enabled in the instant disclosure are outlined above. It is unpredictable based on the instant disclosure which other amino acids can be used for substitutions and at what positions.

Therefore, one of ordinary skill would require guidance, beyond that provided, to make a DNA encoding a mutant GFP having an undefined homology to SEQ ID NOs: 5 or 6 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites positions 64 and 65 in a mutant GFP without reciting SEQ ID NO: of the sequence where the residues numbered 64 and 65 are located. It is confusing because various numberings are used to describe the amino acid sequence of the wild type GFP from *Aequorea victoria* alone (for example, SEQ ID NO: 4 herein and SEQ ID NO: 2 of US Patent 6, 027,881 (form PTO-1449 filed 7/9/04, reference AG1)). Furthermore, GFPs from various sources are known in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Delagrave et al.

Delagrave et al. (form PTO-1449 filed July 9, 2004, reference AR3) teach a DNA encoding GFP mutant F64L/S65L (page 152, Table 1, RSGFP2). This mutant meets limitations of claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Delagrave et al.

This rejection is over mutant GFPs that differ from the wild type *A. victoria* GFP by mutations at positions 64 and 65. Such mutants are enabled and are not included in the enablement rejection above.

The teachings of Delagrave et al. are outlined above. They teach that various 64/65 GFP mutants have fluorescent properties (page 152, Table 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce double GFP mutants comprising various other double 64/65 GFP mutants. One of ordinary skill in the art would have been motivated to do so in order to find double 64/65 GFP mutants that have different fluorescent properties because such mutants can be used for protein localization and trafficking. One of ordinary skill in the art would have a reasonable expectation that other double 64/65 GFP mutants would have useful fluorescent properties and testing of even all possible 64/65 mutants does not require undue experimentation in view of the limited number of the double 64/65 GFP mutants that can be made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cormack et al.

This rejection is over mutant GFPs that differ from the wild type *A. victoria* GFP by mutations at positions 64 and 65. Such mutants are enabled and are not included in the enablement rejection above.

Cormack et al. (US Patent 5,804,387, form PTO-1449 filed July 9, 2004, reference AD1) teach a DNA encoding GFP mutant F64L/S65T (GFP mut1) that has enhanced fluorescence compared with the wild type GFP (abstract; Figures 4-5; column 3). They teach that preferable mutations at position 65 are S65T or S65A (column 3, line 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce double GFP mutants comprising S65T or S65A coupled with any amino acid substituted for F64 as suggested by Cormack et al. One of ordinary skill in the art would have been motivated to do so in order to find double 64/65 GFP mutants that have different fluorescent properties because such mutants can be used for protein localization and trafficking. One of ordinary skill in the art would have a reasonable expectation that other double 64/65 GFP mutants would have useful fluorescent properties and testing of even all possible 64/65 GFP mutants does not require undue experimentation in view of the limited number of the double 64/65 GFP mutants that can be made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 14 of U.S. Patent No. 6,638,732. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-3 and 14 of U.S. Patent No. 6,638,732 are drawn to a DNA encoding SEQ ID NOs:5 and 6 and a humanized DNA encoding SEQ ID NOs:5 and 6. Said DNAs meet the limitations of claim 1 of the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

January 7, 2005